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FORD, VANESSA L	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/725,188	SIN ET AL.	
	Examiner	Art Unit	
	Vanessa L. Ford	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 May 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-48* is/are pending in the application.

4a) Of the above claim(s) *23-26 and 37-44* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-22,27-36 and 45-48* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *01 December 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This action is responsive to Applicant's after-final amendment and remarks filed May 16, 2007. Upon further review and consideration the finality of the Office action submitted February 12, 2007 is withdrawn. A non-final action is set forth below:

Rejections Withdrawn

2. In view of Applicant's After-Final Amendment and Response the following rejections are withdrawn:

a) rejection of claims 1-3, 5-6, 10, 27-29 and 48 under 35 U.S.C. 102(b), pages 8-10, paragraph 5 of the Final Office action mailed February 12, 2007.

b) rejection of claims 1-6, 10 27-29, 35-36 and 48 under 35 U.S.C. 103(a), pages 11-13, paragraph 7 of the Final Office action mailed February 12, 2007.

c) rejection of claims 7-9 under 35 U.S.C. 103(a), pages 14-15, paragraph 8 of the Final Office action mailed February 12, 2007.

d) rejection of claims 1-3, 5-6, 10, 15-16, 20-21, 27-36, 45 and 48 under 35 U.S.C. 103(a), pages 15-18, paragraph 9 of the Final Office action mailed February 12, 2007.

e) rejection of claims 11-13 under 35 U.S.C. 103(a), pages 18-19, paragraph 10 of the Final Office action mailed February 12, 2007.

f) rejection of claims 11-13 under 35 U.S.C. 103(a), pages 20-22, paragraph 11 of the Final Office action mailed February 12, 2007.

Rejections Maintained

3. The rejection under 35 U.S.C. 112 first paragraph is maintained for claim 20 for the reasons set forth on pages 10-11, paragraph 6 of the Final Office Action.

The rejection was on the grounds that The rejection was on the grounds that the claims are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the recombinant protein major adhesion protein of *Aeromonas hydrophila* (AHMA) (pQE-AHMA) which corresponds to SEQ ID NO:8 does not reasonably provide enablement for derivatives of the recombinant protein major adhesin protein of *Aeromonas hydrophila*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification defines the term "fragments" as any polypeptides with exemplary conservative substitutions in an immuno-interactive polypeptide (page 8). The specification fails to provide a structure for the, derivatives of the recombinant protein major adhesin protein of *Aeromonas hydrophila.*

The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of proteins broadly encompassed by the claims and the claims broadly encompass a significant number of inoperative species. Since the amino acid sequence of the protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and still retain similar activity requires a knowledge with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expected intolerant to modification) and detailed knowledge of the ways in which the protein's structure relates to function. However, the problem of the prediction of protein's structure from mere sequence data of a single protein and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein and finally what changes can be tolerated with respect thereto is extremely complex and outside of the realm of routine experimentation.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen multiple substitutions or multiple modifications of other types and the positions within the protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining similar activity are limited in any polynucleotide and the result of such modifications is unpredictable based on the instant disclosure. One skilled in the art would expect any tolerance to modifications, e.g., multiple substitutions. The sequence of some proteins is highly conserved and one skilled in the art would not expect tolerance to any amino acid modification in such protein.

Thomas E. Creighton, in his book, "*Proteins: Structures and Molecular Properties, 1984*", (page 315) teaches that variation of the primary structure of a protein

can result in an instable molecule. He teaches that a single amino acid change can cause a mutant hemoglobin to have lower stabilities due to any of several causes: 1) alteration of close-packing of the interior; loss of one group that normally participates in a hydrogen bond or salt bridge; 2) the introduction of a charged or polar group into the interior or the insertion into a helical region of a proline residue, which must distort the alpha-helix; 3) while sometimes radical changes of surface groups, even introduction of a non-polar side chain- have no great effect on stability.

Thomas E. Creighton, in his book *"Protein Structure: A Practical Approach, 1989; pages 184-186"* teaches that present day site directed mutagenesis of a gene allows any amino acids in a protein sequence to be changed to any other, as well as introducing deletions and insertions". The reference goes on to teach that it is difficult to know which amino acid to change and which is the best residue to substitute for the desired functional and structural effect.

Nosoh, Y. et al in *"Protein Stability and Stabilization through Protein Engineering, 1991" (chapter 7, page 197, second paragraph)* adds support to Thomas E. Creighton, by teaching that results so far accumulated on the stability and stabilization of proteins appear to indicate that the strategy for stabilizing proteins differ from protein to protein and that any generalized mechanisms for protein stability have not yet been presented.

Factors to be considered in determining whether undue experimentation is required are set forth in In re Wands 8 USPQ2d 1400. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and (8) the breadth of the claims.

Applying the above test to the facts of record, it is determined that 1) no declaration under 37 C.F.R. 1.132 or other relevant evidence has been made of record establishing the amount of experimentation necessary, 2) insufficient direction or guidance is presented in the specification with respect to selecting other proteins having claimed functional features, 3) the relative skill of those in the art is commonly recognized as quite high (post-doctoral level). One of skill in the art would require guidance, in order to make or use proteins that are derivatives of the recombinant protein major adhesin protein of *Aeromonas hydrophila* in a manner reasonable in correlation with the scope of the claims. Without proper guidance, the experimentation is undue.

The Applicant has not provided sufficient guidance to enable one of skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any number of additions, deletions or substitutions. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970). Without such guidance, the changes which can be made in the amino acid's structure and still maintain activity is unpredictable and the experimentation left those skilled in the art is unnecessarily and improperly, extensive and undue. See Amgen Inc v Chugai Pharmaceutical Co Ltd. 927 F 2d 1200, 18 USPQ2d 1016 (Fed. Cir. 1991) at 18

USPQ2d 1026-1027 and Exparte Forman, 230 U.S. P.Q. 546(Bd. Pat=. App & int. 1986).

Applicant's Arguments

Applicant disagrees with the Examiner's finding that the specification fails to describe immunoepitopes or fragments that would be protective. Applicant urges that one of ordinary skill in the art could, by routine experimentation follow the methods as set forth in the specification (Examples V-VII) to determine whether the fragments of SEQ ID Nos:2, 4 or 8 were immunogenic. Applicant urges that in the interest of advancing prosecution, Applicant has amended the claims to remove immunogenic fragments.

Examiners Response to Applicant

Applicant's arguments filed May 16, 2007 have been fully considered but they are not persuasive. Claim 20 recites "immunogenic fragments". The claims encompass fragments of SEQ ID Nos. 2, 4, 6 and 8 and combinations thereof which are not defined. The instant specification has not taught which amino acids are deleted or substituted in the amino acid sequence to arrive at a fragment that is encompassed by the claimed invention. This rejection is maintained for the reason of record set forth in the Final Office action mailed February 12, 2007.

4. The rejection under 35 U.S.C. 112 second paragraph is maintained for claim 48 the reasons set forth on page 10, paragraph 9 of the previous Office Action.

The rejection was on the grounds that claim 48 recites the term "predetermined volume". It is unclear as to what the applicant is referring? Clarification as to the meaning of this phrase is required.

Applicant's Arguments

Applicant urges that one of ordinary skill in the art would understand the meaning of the phrase "predetermined volume". Applicant urges that they have amended the claims to recite "immunologically sufficient amount".

Examiners Response to Applicant

Applicant's arguments filed May 16, 2007 have been fully considered but they are not persuasive.

It is the Examiner's position that the phrase "predetermined volume" is vague and indefinite. The metes and bounds of this phrase cannot be determined because the amount or range of the "predetermined" amount would change depending on the subject in which it is administered. It should be noted that claim 48, lines 11 and 13 still recites "predetermined volume". Thus, this rejection is maintained.

New Grounds of Rejection

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

5. Claim 2 is indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 2 depends from claim 1. Claim 2 recites "the recombinant protein fragments". There is insufficient antecedent basis for this limitation in the claim 1. Correction is required.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 1-3, 5-6 and 10 are rejected under 35 U.S.C. 103(a) unpatentable over Fang et al *(Journal of Fish Diseases, 2000, 23, 137-145)* in view of Yang et al *(U.S. Patent No. 6,872,386 published March 29, 2005).*

Claims 1-3, 5-6 and 10 are drawn to an oral vaccine comprising in an orally suitable formulation, at least one of isolated recombinant adhesion protein of *Aeromonas hydrophila* (AHMA) selected from the group consisting of isolated recombinant adhesion proteins having the amino acid sequence as set forth in any one of SEQ Id Nos: 2, 4, or 8, wherein said vaccine is capable, by oral administration in an

immunologically sufficient amount of effecting immunization an animal against *Aeromonas hydrophila.*

Fang et al teach a vaccine composition comprising the 43 kDa major adhesin protein isolated from *Aeromonas hydrophila* and Freund's complete adjuvant (see the Abstract and page 139). Fang et al teach that the vaccine composition contained 150 $\mu g\ mL^{-1}$ of the protein (page 139). Claim limitations such as "wherein the proportion of water and oil in the emulsion further comprise 1:2, "wherein the proportion of water in the emulsion is equal" are being viewed as limitations of experimental design choice.

Fang et al do not teach "oral administration".

Yang et al teach that oral administration has advantages because it is non-stressful, requires little labor, and can be applied at a large scale. Yang et al discloses oral vaccines that are effective, although oral vaccines taught in the art have not been successful (column 1). Yang et al teach that the oral vaccines of the invention comprise more than one antigen. Yang et al teach oral vaccines that comprise multiple antigens produce immune response from the same or different pathogens (column 2).

It would be prima facie obvious at the time the invention was made to prepare a vaccine that is suitable for oral administration because Yang et al teach that oral administration has advantages because it is non-stressful, requires little labor, and can be applied at a large scale. It would be expected absent evidence to the contrary, that the vaccine as taught by Fang et al would be effective if formulated in an oral suitable form because Yang et al have demonstrated that orally administered vaccines are effective in treating aquatic animals.

7. Claim 4 is rejected under 35 U.S.C. 103(a) unpatentable over Fang et al *(Journal of Fish Diseases, 2000, 23, 137-145)* in view of Yang et al *(U.S. Patent No. 6,872, 386 published March 29, 2005)* as applied to claims 1-3, 5-6 and 10 above and further in view of Chen et al *(U.S. Patent No. 6,720, 001 B1, published April 13, 2004)*.

Claim 4 is drawn to the oral vaccine of claim 3 further comprising palm oil.

Fang et al and Yang et al as combined above do not teach palm oil.

Chen et al teach the that organic oil such as palm oil can be used to provide improved delivery of polyfunctional active ingredients (Abstract, columns 5 and 6). Chen et al teach that the compositions of the invention that contain organic oils such as palm oil are stable compositions (column 5).

It would be *prima facie* obvious at the time the invention was made to add the palm oil as taught by Chen et al to the vaccine composition of Fang et and Yang et al as combined above because Chen et al teach the that organic oil such as palm oil can be used to provide improved delivery of polyfunctional active ingredients (columns 5 and 6). It would be expected barring evidence to the contrary that a vaccine comprising palm oil would be effective stabilizing vaccines at improving delivery of polyfunctional active ingredients.

8. Claims 7-9 are rejected under 35 U.S.C. 103(a) unpatentable over Fang et al *Journal of Fish Diseases, 2000, 23, 137-145)* in view of Yang et al *(U.S. Patent No.*

6,872, 386 published March 29, 2005) as applied to claims 1-3, 5-6 and 10 and further in view of Calanchi et al *(U.S. Patent No. 5,008,117, published April 16, 1991)*.

Claims 7-9 are drawn to the oral vaccine of claim 2 further mixed with a binding agent, wherein the binding agent comprises particulate feed material and wherein the binding agent comprises high viscosity carboxymethylcellose.

The teachings of Fang et al and Yang et al have been described previously (paragraph 5 above).

Fang et al and Yang et al as combined above do not teach binding agents such as carboxymethylcellulose.

Calanchi et al teach that binding agents such as carboxymethylcellulose (column 3). Calanchi et al teach that binders are soluble in water and solvents (column 3). Calanchi et al teach that binders are often used to thicken the composition (column 4). Calanchi et al teach using these thickeners or binding agents in pharmaceutical compositions (column 2, examples and claims).

It would be *prima facie* obvious at the time the invention was made to add carboxymethylcellulose as taught by Calanchi et al to the vaccine composition of Wolf-Fang et al and Yang et al as combined above because Calanchi et al teach that binders are often used to thicken the composition and have the property of dispersing and dissolving quickly in water or aqueous vehicles (see the Abstract). It would be expected barring evidence to the contrary that a vaccine comprising binding agents such as carboxymethylcellulose would be effective in making the components of the composition easily to disperse and dissolve quickly in water or aqueous vehicles.

9. Claims 11-12, 15-16, 20, 27-32, 35-36 and 48 are rejected under 35 U.S.C. 103(a) unpatentable over Fang et al (*Journal of Fish Diseases, 2000, 23, 137-145)* in view of Yang et al *(U.S. Patent No. 6,872, 386 published March 29, 2005) as* applied to claims 1-3, 5-6 and 10 above and further in view of Wang et al *(Fish Shellfish Immunol, Nov. 2002;13(5):337-50(Abstract only).*

Claims 11-12, 15-16, 20, 27-32, 35-36 and 48 are drawn to the oral vaccine of claim 1 further comprising recombinant protein comprising immobilization antigen repeat I of *Ichthyophythirius multifiliis.*

The teachings of Fang et al and Yang et al have been described previously (paragraph 5 above).

Fang et al and Yang et al as combined above do not teach a vaccine comprising the immobilization antigen repeat I of *Ichthyophythirius multifiliis.*

Wang et al teach a vaccine composition comprising the immobilization antigen repeat I of *Ichthyophythirius* and Freund's incomplete adjuvant (see the Abstract). Wang et al teach that fish immunized with *Ichthyophythirius multifiliis* (the antigen developed high titers of serum immobilized antibodies (see the Abstract). Wang et al teach that this study shows there is a clear role for the immobilization antigen repeat I of *Ichthyophythirius* in protection (see the Abstract). The claim limitation "recombinant" is being viewed as a process limitation.

Regarding the specific dosages or ranges listed in the instant claims, MPEP 2144.05 states, "Generally, differences in concentration or temperature will not support

the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955) (Claimed process which was performed at a temperature between 40°C and 80°C and an acid concentration between 25% and 70% was held to be *prima facie* obvious over a reference process which differed from the claims only in that the reference process was performed at a temperature of 100°C and an acid concentration of 10%.); see also *Peterson*, 315 F.3d at 1330, 65 USPQ2d at 1382 ("The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages."); *In re Hoeschele*, 406 F.2d 1403, 160 USPQ 809 (CCPA 1969) (Claimed elastomeric polyurethanes which fell within the broad scope of the references were held to be unpatentable thereover because, among other reasons, there was no evidence of the criticality of the claimed ranges of molecular weight or molar proportions.). For more recent cases applying this principle, see *Merck & Co. Inc. v. Biocraft Laboratories Inc.*, 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), *cert. denied*, 493 U.S. 975 (1989); *In re Kulling*, 897 F.2d 1147, 14 USPQ2d 1056 (Fed. Cir. 1990); and *In re Geisler,* 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997)."

It would be *prima facie* obvious at the time the invention was made to add the immobilization antigen repeat I of *Ichthyophythirius* as taught by Wang et al to the vaccine composition of Yang et al because Yang et al teach that the oral vaccine of

the invention comprise multiple antigens that induce immune response against the same or different antigens. It would be expected barring evidence to the contrary that a vaccine comprising proteins from *Aeromonas hydrophila* and immobilization antigen repeat I of *Ichthyophythirius* would be effective in protecting against a broad spectrum of fish diseases.

10. Claims 13-16 are rejected under 35 U.S.C. 103(a) unpatentable over Fang et al *(Journal of Fish Diseases, 2000, 23, 137-145)*, Yang et al *(U.S. Patent No. 6,872, 386 published March 29, 2005)* and Wang et al *(Fish Shellfish Immunol., Nov. 2002;13(5):337-50) (Abstract only)* as applied to claims 1-3, 5-6, 10-12, 15-16, 20, 27-32, 35-36 and 48 above and further in view of Chen et al *(U.S. Patent No. 6,720, 001 B1, published April 13, 2004)*.

Claims 13-16 are drawn to the vaccine of claim 12 further wherein said emulsifying oil comprises organic oil, wherein said emulsifying oil comprises palm oil, wherein the proportion of water and oil in the emulsion is the ratio 1:2 and wherein the proportion of water and oil in the emulsion is equal.

The teachings of Fang et al, Yang et al and Wang et al have been described previously (paragraph 8 above).

Fang et al, Yang et al and Wang et al as combined above do not teach organic oil or palm oil.

Chen et al teach that organic oil such as palm oil can be used to provide improved delivery of polyfunctional active ingredients (columns 5 and 6). Chen et al

teach that the compositions of the invention that contain organic oils such as palm oil are stable compositions (column 5).

It would be *prima facie* obvious at the time the invention was made to add the palm oil as taught by Chen et al to the vaccine composition of Fang et al, Yang et al and Wang et al as combined above because Chen et al teach the that organic oil such as palm oil can be used to provide improved delivery of polyfunctional active ingredients (columns 5 and 6). It would be expected barring evidence to the contrary that a vaccine comprising palm oil would be effective stabilizing vaccines at improving delivery of polyfunctional active ingredients.

11. Claims 17-19 are rejected under 35 U.S.C. 103(a) unpatentable over Fang et al (*Journal of Fish Diseases, 2000, 23, 137-145),* Yang et al *(U.S. Patent No. 6,872, 386 published March 29, 2005)* and Wang et al *(Fish Shellfish Immunol., Nov. 2002;13(5):337-50)(Abstract only)* as applied to claims 1-3, 5-6, 10-12, 15-16, 20, 27-32, 35-36 and 48 above and further in view of Calanchi et al *(U.S. Patent No. 5,008,117, published April 16, 1991).*

Claims 17-19 are drawn to the oral vaccine of claim 12 further mixed with a binding agent, wherein the binding agent comprises particulate feed material and wherein the binding agent comprises high viscosity carboxymethylcellose.

The teachings of Fang et al, Yang et al and Wang et al have been described previously (paragraph 8 above).

Fang et al, Yang et al and Wang et al as combined above do not teach a vaccine comprising carboxymethylcellulose.

Calanchi et al teach that binding agents such as carboxymethylcellulose (column 3). Calanchi et al teach that binders are soluble in water and solvents (column 3). Calanchi et al teach that binders are often used to thicken the composition (column 4). Calanchi et al teach using these thickeners or binding agents in pharmaceutical compositions (column 2, examples and claims).

It would be *prima facie* obvious at the time the invention was made to add carboxymethylcellulose as taught by Calanchi et al to the vaccine composition of Wolf-Fang et al, Yang et al and Wang et al as combined above because Calanchi et al teach that binders are often used to thicken the composition and have the property of dispersing and dissolving quickly in water or aqueous vehicles (see the Abstract). It would be expected barring evidence to the contrary that a vaccine comprising binding agents such as carboxymethylcellulose would be effective at making the components of the composition easily to disperse and dissolve quickly in water or aqueous vehicles.

12. Claims 21 and 33-36 are rejected under 35 U.S.C. 103(a) unpatentable over Fang et al *Journal of Fish Diseases, 2000, 23, 137-145)* in view of Yang et al *(U.S. Patent No. 6,872, 386 published March 29, 2005)* as applied claims 1-3, 5-6 and 10 and further in view of Wolf-Watz et al (*U.S. Patent No. 5,284,653 published February 8, 1994).*

Claim 21 and 33-36 are drawn to the oral vaccine according to claim 1 further comprising an inactivated virus selected from the group consisting of guppy reovirus and guppy nervous necrosis virus.

The teachings of Fang et al and Yang et al have been described previously (paragraph 5 above).

Fang et al and Yang et al do not teach a fish vaccine comprising guppy reovirus and guppy nervous necrosis virus.

Wolf-Watz et al teach a fish vaccine comprising live avirulent invasive for fish pathogenic bacteria for immunization of fish against infectious disease (see the Title and the Abstract). Wolf-Watz et al teach that viruses such as infectious pancreatic necrosis virus (guppy reovirus) and infectious hematopoietic necrosis virus may apart of the vaccine of the invention (column 6). Wolf-Watz et al teach that the bacteria of the invention contains $1x10^2$-$1x10^8$ bacteria/ml (column 8). Wolf-Watz et al teach that the vaccine of the invention can be added to fish feed (column 8).Wolf-Watz et al teach that the invention contemplates vaccines comprising bacteria the carry multiple determinants from different pathogenic fish and capable of expressing hybrid (fusion) determinants (column 7).

Regarding the specific dosages or ranges listed in the instant claims, MPEP 2144.05 states, "Generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or

workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955) (Claimed process which was performed at a temperature between 40°C and 80°C and an acid concentration between 25% and 70% was held to be *prima facie* obvious over a reference process which differed from the claims only in that the reference process was performed at a temperature of 100°C and an acid concentration of 10%.); see also *Peterson*, 315 F.3d at 1330, 65 USPQ2d at 1382 ("The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages."); *In re Hoeschele*, 406 F.2d 1403, 160 USPQ 809 (CCPA 1969) (Claimed elastomeric polyurethanes which fell within the broad scope of the references were held to be unpatentable thereover because, among other reasons, there was no evidence of the criticality of the claimed ranges of molecular weight or molar proportions.). For more recent cases applying this principle, see *Merck & Co. Inc. v. Biocraft Laboratories Inc.*, 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), *cert. denied*, 493 U.S. 975 (1989); *In re Kulling*, 897 F.2d 1147, 14 USPQ2d 1056 (Fed. Cir. 1990); and *In re Geisler,* 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997)."

It would be *prima facie* obvious at the time the invention was made to add the guppy reovirus as taught by Wolf-Watz et al to the vaccine composition of Fang et al and Yang et al as combined above because Yang et al teach oral vaccines that comprise multiple antigens produce immune response from the same or different pathogens (column 2) and Wolf-Watz et al teach that the vaccine of the invention may comprise one or more antigens that are pathogenic to fish to produce a vaccine that

provides broad spectrum protection against a range of fish pathogens (column 7). It would be expected barring evidence to the contrary that a vaccine comprising proteins from multiple antigens would be effective in protecting against a broad spectrum of fish diseases.

13. Claim 22 is rejected under 35 U.S.C. 103(a) unpatentable over Fang et al *(Journal of Fish Diseases, 2000, 23, 137-145)* in view of Yang et al *(U.S. Patent No. 6,872, 386 published March 29, 2005)* as applied to claims 1-3, 5-6, and 10 and further in view of Morinigo et al *(Bulletin of the European Association of Fish Pathologists, Nov.2, 2002, Vol. 22, No.5, p. 298-303)*.

Claim 22 is drawn to the oral vaccine according to claim 1 further comprising bacterial antigens of killed bacteria selected from the group consisting of bacterial antigens or killed bacteria selected from the group consisting of *Shewanella putrefaciens, Pseudomonas florescens, Vibrio alginolyticus* and *Flexibacter columnaris.*

The teachings of Fang et al and Yang et al have been described previously (paragraph 5 above).

Fang et al and Yang et al do not teach vaccines comprising bacterial antigens or killed bacteria selected from the group consisting of *Shewanella putrefaciens, Pseudomonas florescens, Vibrio alginolyticus* and *Flexibacter columnaris.*

Morinigo et al teach that a divalent vaccine composition comprising *Vibrio alginolyticus* and *Photobacterium damselae subsp. Piscicida.* Morinigo et al teach that

the concentration of protein 800 mg ml^{-1} (page 299).Morinigo et al teach that high protection was conferred by the divalent vaccine (page (302).

It would be *prima facie* obvious at the time the invention was made to add the *Vibrio alginolyticus* and *Photobacterium damselae subsp. Piscicida* antigens as taught by Morinigo et al to the vaccine composition of Fang et al and Yang et al as combined above because Yang et al teach oral vaccines that comprise multiple antigens produce immune response from the same or different pathogens (column 2). It would be expected barring evidence to the contrary that a vaccine comprising proteins from *Aeromonas hydrophila* and *Vibrio alginolyticus* and *Photobacterium damselae subsp. Piscicida* antigens would be effective in protecting against a broad spectrum of fish diseases.

14. Claim 45 is rejected under 35 U.S.C. 103(a) unpatentable over Fang et al (*Journal of Fish Diseases, 2000, 23, 137-145)*, Yang et al *(U.S. Patent No. 6,872, 386 published March 29, 2005)* and Wang et al *(Fish Shellfish Immunol., Nov. 2002;13(5):337-50)*(Abstract only) as applied to claims 1-3, 5-6, 10-12, 15-16, 20, 27-32, 35-36 and 48 above and in further view of Wolf-Watz et al (*U.S. Patent No. 5,284,653 published February 8, 1994)*.

Claims 45 is drawn to the oral vaccine of claim 11 further comprising an inactivated virus selected from the group consisting of guppy reovirus and guppy nervous necrosis virus.

The teachings of Fang et al, Yang et al and Wang et al have been described previously (paragraph 8 above).

Fang et al, Yang et al and Wang et al as combined above do not teach guppy reovirus and guppy nervous necrosis virus.

Wolf-Watz et al teach a fish vaccine comprising live avirulent invasive bacteria (see the Title and the Abstract). Wolf-Watz et al teach that viruses such as infectious pancreatic necrosis virus (guppy reovirus) and infectious hematopoietic necrosis virus may apart of the vaccine of the invention (column 6). Wolf-Watz et al teach that the bacteria of the invention contains $1x10^2$-$1x10^8$ bacteria/ml (column 8). Wolf-Watz et al teach that the vaccine of the invention can be added to fish feed (column 8).Wolf-Watz et al teach that the invention contemplates vaccines comprising bacteria the carry multiple determinants from different pathogenic fish and capable of expressing hybrid (fusion) determinants (column 7).

It would be *prima facie* obvious at the time the invention was made to add the guppy reovirus as taught by Wolf-Watz et al to the vaccine composition of Fang et al, Yang et al and Wang et al as combined above because Yang et al teach oral vaccines that comprise multiple antigens produce immune response from the same or different pathogens (column 2) and Wolf-Watz et al teach that the vaccine of the invention may comprise one or more antigens that are pathogenic to fish to produce a vaccine that provides broad spectrum protection against a range of fish pathogens (column 7). It would be expected barring evidence to the contrary that a vaccine comprising proteins

from multiple antigens would be effective in protecting against a broad spectrum of fish diseases.

15. Claim 46 is rejected under 35 U.S.C. 103(a) unpatentable over Fang et al (*Journal of Fish Diseases, 2000, 23, 137-145)*, Yang et al *(U.S. Patent No. 6,872, 386 published March 29, 2005)* and Wang et al *(Fish Shellfish Immunol., Nov. 2002;13(5):337-50)* as applied to claims 1-3, 5-6, 10-12, 15-16, 20, 27-32, 35-36 and 48 above and in further view of Morinigo et al *(Bulletin of the European Association of Fish Pathologists, Nov.2, 2002, Vol. 22, No.5, p. 298-303).*

Claims 46 is drawn to the oral vaccine of claim 11 further comprising bacterial antigens of killed bacteria selected from the group consisting of bacterial antigens or killed bacteria selected from the group consisting of *Shewanella putrefaciens, Pseudomonas florescens, Vibrio alginolyticus* and *Flexibacter columnaris.*

The teachings of Fang et al, Yang et al and Wang et al have been described previously (paragraph 8 above).

Fang et al, Yang et al and Wang et al do not teach bacterial antigens or killed bacteria selected from the group consisting of *Shewanella putrefaciens, Pseudomonas florescens, Vibrio alginolyticus* and *Flexibacter columnaris.*

Morinigo et al teach that a divalent vaccine composition comprising *Vibrio alginolyticus* and *Photobacterium damselae subsp. Piscicida.* Morinigo et al teach that the concentration of protein 800 mg ml^{-1} (page 299).Morinigo et al teach that high protection was conferred by the divalent vaccine (page (302).

It would be *prima facie* obvious at the time the invention was made to add the *Vibrio alginolyticus* and *Photobacterium damselae subsp. Piscicida* antigens as taught by Morinigo et al to the vaccine composition of Fang et al, Yang et al and Wang et al as combined above because Yang et al teach oral vaccines that comprise multiple antigens produce immune response from the same or different pathogens (column 2). It would be expected barring evidence to the contrary that a vaccine comprising proteins from *Aeromonas hydrophila* , the immobilization antigen repeat I of *Ichthyophythirius, Vibrio alginolyticus* and *Photobacterium damselae subsp. Piscicida* antigens would be effective in protecting against a broad spectrum of fish diseases.

Status of Claims

16. No claims allowed.

Conclusion

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Vanessa L. Ford whose telephone number is (571) 272-0857. The examiner can normally be reached on 9 am- 6 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on (571) 272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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August 17, 2007

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